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Appropriateness and complications of androgen deprivation therapy for prostate cancer: Can we do better? A retrospective observational analysis from a referral center

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Abstract

Introduction: Androgen deprivation therapy (ADT) is the key of medical treatment for advanced prostate cancer (PCa), especially in elderly patients. However, the adherence of ADT prescription to current guidelines is not optimal and must be balanced against possible side effects. Aim of this study was to evaluate the prescriptive appropriateness of ADT and ADT-related adverse events in a referral center for PCa.

Methods: Five hundred fifty six patients who received an outpatient prescription for ADT from 2014 to 2018 were retrospectively identified from an administrative database. Only standard ADT was considered, including GnRH agonists, GnRH antagonists, and antiandrogens. Prescriptive appropriateness was defined according to the last European Association of Urology (EAU) guidelines. Our cohort was stratified according to age categories and patient follow-up was updated.

Results: Four hundred twenty five patients were available for analysis. Mean age was 80 years; 96.3% of our patients fell in the "elderly" category. There was a predominance of GnRH agonists over the antagonists (84.9% vs 13%). 15.5% of ADTs did not have an appropriate indication according to guidelines. Patient compliance to ADT was evaluated as good in 372 (87.5%) cases. ADT-related complications were detected in 166 (39%) patients: bone, cardiovascular, and other complications were reported in 7.3%, 8.9%, and 19% of patients. Progression of disease was noted in 165 (38.8%) cases during ADT. At last follow-up, 124 (30.1%) patients were deceased.

Conclusions: In a referral center, most ADT prescriptions followed EAU guidelines, but a non-negligible proportion still did not fall within these indications, exposing patients to unnecessary side effects. Compliance to ADT was generally good with a predominant use of GnRH agonists. Tolerance to ADT was fair, even if standardized reports were lacking.

Keywords

Hormonal therapy, ADT, agonists, antagonists, indication, complication

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Introduction

Androgen deprivation therapy (ADT) is the key of medical treatment of advanced prostate cancer (PCa). Although primarily indicated for systemic PCa, ADT is also used in other clinical settings, including combination therapy in high risk patients undergoing radiotherapy, lymph node

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metastasis after radical prostatectomy, or locally advanced cancers unfit for radical treatment.[1]

However, despite ADT use is accurately described in contemporary guidelines, a significant rate of inappropriate prescription is still observed. In this regard, the Italian CHOICE study reported a discordance of ADT prescription to EAU guidelines in more than one out of four men.[2]

Elderly people represent the category of patients at higher risk of receiving an inappropriate indication to ADT, sometimes administered only to reassure patients with elevated PSA.

Considering that PCa is the second most frequent malignancy in men worldwide,[3] a huge number of patients is annually treated with ADT, being it appropriately or inappropriately prescribed, and consequently exposed to its adverse effects. Among these, there are hot flushes, loss of libido, sexual dysfunction, fatigue, anemia, bone loss, and metabolic changes that include weight gain, insulin resistance, dyslipidemia, and lipid alterations, contributing to a significantly increased risk of diabetes and cardiovascular (CV) events.[4–8] Bone changes due to ADT have been well demonstrated and preventive measures have been suggested to avoid skeletal-related events (SREs), including physical exercise, calcium and vitamin D supplements, and antiresorptive agents such as zoledronate and denosumab.[9] As for CV events, data on CV mortality remain equivocal, but special attention to the risk-to-benefit ratio of ADT agonists is advocated in patients with higher risk of CV complications[10–16]; among ADT types, a better CV safety profile for GnRH antagonists has recently been hypothesized.[15]

So far, existing evidence is not conclusive and particular focus should be given to the elderly patients, more exposed to inappropriate prescription and adverse events that might impair their quality of life (QoL) or even shorten their life expectancy. To shed light on this issue, we structured a study with the aim to evaluate the prescriptive appropriateness of ADT and ADT-related adverse events in a contemporary cohort of patients treated in a referral center for PCa, stratified by age.

Materials and methods

After Institutional Review Board approval, 556 patients who received an outpatient prescription for ADT for PCa from 2014 to 2018 were retrospectively identified from an administrative database. All patients were routinely followed at our institution with urological consultations scheduled according to clinical needs. Follow-up of these patients was updated by performing in person or telephonic consultations and by reviewing clinical records. Men untraceable at follow-up were excluded.

Endpoints of our study were (i) the assessment of the prescriptive appropriateness of ADT according to the current EAU criteria and (ii) the evaluation of the incidence of ADT-related adverse events, with particular focus on bone and CV events.

Statistical analyses were performed with SPSS version 26.0 (IBM Corp, Armonk, NY, USA). Quantitative data are shown as mean and standard deviation (SD), while qualitative data are shown as median (interquartile range). Chi square was calculated to compare our results with those of CHOICE.[2]

Definition of ADT

For the present study, we only considered standard ADT, including: *GnRH agonists* (ATC code L02AE: buserelin L02A01, leuprorelin L02A02, goserelin L02A03, triptorelin L02A04, hystrelin L02A05); *GnRH antagonists* (ATC code L02BX: degarelix L02BX02); *antiandrogens* (ATC code L02BB: bicalutamide, flutamide).

Definition of prescriptive appropriateness of ADT

ADT prescription was defined appropriate or inappropriate following European Association of Urology (EAU) guidelines: ADT monotherapy should not be used in asymptomatic localized PCa; ADT can be used in concomitance with radiotherapy in localized or locally advanced PCa; ADT monotherapy can be offered to patients not fit or not accepting local treatment, either symptomatic or asymptomatic, with PSA doubling time (DT) <12 months or PSA >50 ng/ml or poorly differentiated tumor; ADT can be used as adjuvant treatment in N+ patients after surgery; ADT should not be used as standard in patients with biochemical relapse after radical treatment, especially if M0 with PSA-DT >12 months; ADT is first-line systemic treatment in M1 PCa; patients with castrate-resistant PCa (CRPC) must continue first-line ADT. All ADT prescriptions which were not in accordance with the EAU guidelines were considered as inappropriate.

Definition of ADT-related complications

Compliance was defined as adherence to treatment following the urologist's indications. ADT-related complications were classified as follows:

- *Bone complications*: pathologic fractures, severe osteoporosis or osteopenia (new-onset or worsening during ADT).
- *CV complications*: acute myocardial infarction, ischemic coronary disease, stroke, cardiac failure, arterial embolic and thrombotic events.
- *Other complications*: new-onset diabetes mellitus or dyslipidemia (or worsening during ADT), hyporegenerative anemia, hot flushes, fatigue.

Definition of "elderly"

It is not easy to define an adequate threshold to consider an individual to be "elderly," given the continuous increase in longevity of the global population: it is estimated that in the European Union around 63.9 million people will be octogenarian by 2080.[17] Nowadays, people are considered "elderly" when they fall outside the so-called working age group, past 65–70 years. For the present study, we have adopted the following age classification: *young*, <65 years; *young old*, 65–74 years; *old old*, 75–84 years; *oldest old*, ⩾85 years. We acknowledge that broad variations characterize these groupings, depending on the individual performance status, comorbidities, and the degree of frailty.

Results

Baseline characteristics

After excluding patients with incomplete clinical or follow-up data, 425 patients were available for analysis. Mean age was 80 years (range 48–99); more in detail, 16 (3.7%) were "young," 85 (20%) "young old," 176 (41.4%) "old old," and 148 (34.8%) "oldest old." Overall, 96.3% of our patients fell in the "elderly" category. Baseline patients characteristics are detailed in Table 1.

Assessment of prescriptive appropriateness

Indications to ADT are shown in Table 2, according to their prescriptive appropriateness. Of note, 15.5% of ADTs did not have an appropriate indication according to EAU guidelines.[1] There was a statistically significant difference between our 15.5% of inappropriate prescriptions as compared to the 26.5% reported in the Italian CHOICE study ($p < 0.00001$).

Assessment of ADT-related complications

Patient compliance to ADT was evaluated as good in 372 (87.5%) of cases. ADT-related complications were detected in 166 (39%) patients and are detailed in Table 3: bone, CV, and other complications were reported in 7.3%, 8.9%, and 19% of patients. During ADT, 48 (11.3%) patients received concomitant bone antiresorptive therapy, 43 with bisphosphonates (10.1%), 5 with denosumab (1.2%). Only 28 (6.6%) patients were addressed to an endocrinologic consultation for metabolic and bone health evaluation during ADT.

Follow-up

Biochemical or clinical progression of disease was noted in 165 (38.8%) cases during ADT. At last follow-up, 289 (69.9%) patients were alive, while 124 (30.1%) deceased. All-cause mortality rates were 6.7% for "young," 29.7%

Table 1. Baseline patients characteristics.

Baseline characteristics ($N = 425$)	
Age, mean (SD)	80.4 (8.2)
Age, median (IQR)	81 (75–86)
Smoker, n (%)	Active: 48 (12.2)
Missing: 33	Ex: 105 (26.8)
Hypertension, n (%)	219 (55.2)
Missing: 28	
Diabetes, n (%)	77 (19.4)
Missing: 29	
Previous cardio/cerebrovascular events, n (%)	156 (38.9)
Missing: 24	
Pre-existing bone disease, n (%)	43 (10.7)
Missing: 25	
PCa features at diagnosis	
ISUP grade, n (%)	
- 1, 2	99 (29.2)
- 3	73 (21.5)
- 4, 5	162 (47.8)
Missing: 86	
PSA median (IQR)	17.9 (8–37.8)
Clinical/Pathologic stage, n (%)	
- T1/T2	92 (37.8)
- T3/T4- N1	151 (62.1)
- M1	103 (42.4)
Missing or "clinical" diagnoses: 182	84 (34.6)
ADT characteristics	
LHRH-agonists/antagonists, n (%)	
- Leuprorelin	253 (59.7)
- Triptorelin	106 (25)
- Goserelin	8 (0.2)
- Degarelix	57 (13.4)
Frequency of ADT administration, n (%)	
- Monthly	188 (44.2)
- Quarterly	235 (55.3)
- Semi-annual	1 (0.2)
Therapy duration, years, mean (SD)	4.3 (4.1)
Therapy duration, years, median (IQR)	3 (2–5)
Therapy type, n (%)	
- continuous	322 (75.7)
- intermittent	103 (24.3)
Switch during therapy, n (%)	71 (19.6)
Missing: 62	
Antiandrogen use (except for flare-up), n (%)	
- Bicalutamide	104 (28.6)
- Flutamide	1 (0.2)
- Cyproterone acetate	1 (0.2)
Missing: 61	
Advanced treatments in case of progression	
Therapy, n (%)	
- Abiraterone	29 (6.8)
- Enzalutamide	39 (9.2)
- Docetaxel	33 (7.7)
- Cabazitaxel	16 (3.7)

Table 2. Appropriateness of ADT.

Appropriate indications: 359 (84.5%)	Inappropriate indication: 66 (15.5%)
ADT concomitant to radiotherapy: 39 (10.8%)	Biochemical recurrence with low PSA or slow PSA-DT after radical treatment: 20 (30.3%)
ADT in high risk/locally advanced PCa in patients unfit for or unwilling radical treatment: 86 (23.9%)	ADT in localized PCa in patients fit for radical treatment: 46 (69.7%)
Pelvic nodal involvement (pN+): 44 (12.2%)	
Extrapelvic nodal/bone/visceral metastases (M1a/b): 122 (33.9%)	
Biochemical recurrence with elevated PSA or PSA-DT < 12 months: 54 (15.0%)	
Local recurrence without other treatment indications: 11 (3.0%)	
Neoadjuvant therapy (clinical trials): 3 (0.8%)	

ADT: androgen deprivation therapy; PCa: prostate cancer.

Table 3. ADT-related complications.

Complications, n (%)		Agonists vs antagonists	Missing
Bone: 31 (7.3)	Osteopenia/osteoporosis: 12	Agonists: 23/344 (6.7%)	31
	Pathologic bone fracture: 19	Antagonists: 8/50 (16%)	
Cardio/cerebrovascular: 35 (8.9)	Acute myocardial infarction: 11	Agonists: 33/343 (9.6%)	34
	Stroke: 9	Antagonists: 2/48 (4.1%)	
	Transitory ischemic attack: 2		
	Cardiac failure: 4		
	Syncope: 1		
	Thrombosis/pulmonary embolism/vasculopathy: 6		
Metabolic/other: 81 (19)	New onset diabetes: 6	Agonists: 70/342 (20.5%)	35
	Hypercholesterolemia, weight gain: 5		
	Fatigue: 27	Antagonists: 11/48 (22.9%)	
	Hot flushes: 29		
	Anemia: 17		
	Gynecomastia: 11		
	Hyperidrosis: 3		
	Diffuse itching: 3		
	Allergy in injection site: 1		

ADT: androgen deprivation therapy.

for "young old," 27.8% for "old old," and 35.7% for "oldest old."

Discussion

ADT is the most commonly used medical treatment for PCa, with proven efficacy when correctly prescribed. As shown by our work and the CHOICE study,[2] however, the indication to ADT is too often inappropriately given, exposing patients to the risk of side effects without any survival benefit, not to speak of economic repercussions, being these high-cost drugs administered for years.

Our analysis showed interesting data about the ADT management by a Italian center referral for PCa.

From an epidemiological point of view, we observed that ADT mainly involves elderly patients, with 96% of our patients being ⩾65 years and 76% of them being "oldest old." These patients need special care even only for their intrinsic frailty. As for baseline comorbidities, more than 50% of our patients had hypertension and roughly 40% had a pre-existing CV or cerebrovascular event. Only a 10% of our cohort had history of osteoporosis, but probably the real data would be higher if a bone densitometry had been performed in all patients.

As for PCa features at diagnosis, an aggressive disease was diagnosed, in the majority of cases, with a Gleason score 8–10, a markedly elevated PSA, or advanced clinical/pathological stages. It is noteworthy to remark that it is often hard to find detailed data about PCa at diagnosis: in the recent past it was not uncommon to start ADT even only in the clinical suspicion of PCa in an elderly patient. In our series, a high percentage of patients did not undergo prostate biopsy before starting systemic treatment. Currently, histological diagnosis and staging examinations are required even in elderly patients, before starting an ADT that might be not necessary or to have access to the novel antiandrogens.

In line with other studies in the literature,[18,19] we showed that GnRH agonists are more used than antagonists (84.9% vs 13%), probably due to old prescriptive habits by treating physicians. ADTs are typically long, more than 4 years on average, while intermittent regimens were adopted in one-fourth of patients, when feasible, with the aim of limiting the side effects.[20] However, no significant difference in terms of complications were reported between intermittent and continuous regimens. When response to ADT was scarce/inadequate, a drug switch was made in 20% of cases, while total androgen blockade was used in 29% of patients, even if we know that this option has only slight survival benefit at the cost of an increase of adverse events.[1]

Thirty percent of our patient deceased during follow-up; unfortunately, in most cases the causes of death were unknown, and we were not able to retrieve this data. Almost 40% of our patients experienced disease progression during ADT, reflecting the aggressiveness of advanced PCa. Nowadays more therapeutic options are available in advanced stages of disease, prolonging survival of PCa patients.

First study endpoint was the assessment of the prescriptive appropriateness of ADT. Our findings of 15.5% of inappropriate prescriptions significantly differ from the 26.5% highlighted in the Italian CHOICE study[2] and possibly reflect a better management in a urological center referral for PCa. However, it is still alarming that 66 patients received an ADT which was not considered adequate according to EAU guidelines,[1] with an unnecessary exposition to ADT side effects and a considerable waste of resources. If we estimate that monthly cost of ADT was around 100€ and mean therapy duration was 4.3 years, the total cost amounts at 340.560€, not to speak of the cost of management of potential adverse events. The 26.5% of discrepancy of CHOICE[2] gives an idea on the amount of money that could be saved at a National level. Among the indications deemed as inappropriate, the most frequent was ADT in elderly patients with localized disease who would have been still fit for a radical treatment. Age alone is not enough to exclude a patient from surgery or radiation therapy: a thorough evaluation must be done including the assessment of comorbidities and frailty status. Another frequent inappropriate indication to ADT was represented by biochemical recurrence with low PSA-DT: these cases, especially in elderly, should undergo a simple surveillance.

Second endpoint of study was the evaluation of ADT-related complications, which obviously affect patient QoL.

Among the most feared complications there are CV events that are associated with the loss of androgens and their cardioprotective action.[5] Multiple observational trials and retrospective studies have linked ADT use to an increased risk of CV events, which might be driven by atherosclerotic plaque instability induced by GnRH agonists.[5,6] In 2010, Food and Drug Administration asked manufacturers of GnRH agonists to add extra safety information concerning the increased risk of diabetes and certain CV diseases, including heart attack, sudden cardiac death, and stroke. Main studies focusing on CV risk are summarized in Table 4. Most of them are concordant in reporting a higher risk of CV events, but a meta-analysis of eight randomized controlled trials (RCT) has not shown any difference in CV mortality between patients receiving ADT or not.[16] Of note, the RCTs included in this meta-analysis were not specifically planned to assess the risk of CV disease and were affected by selection bias, a limited number of CV events, and competing-risk issues. Our study showed only a 8% incidence of CV and cerebrovascular events, but is limited by its retrospective nature and could have missed some CV events not reported in the clinical charts. The lack of data on CV mortality represents another important limitation.

A protective effect of GnRH antagonists on CV risk has been suggested by several studies, especially in patients with pre-existing CV disease (Table 5). The recent meta-analysis of Abufaraj et al.[30] has confirmed this finding, as previously reported by Albertsen et al.[8] in 2014, showing a relative risk of 0.52 for degarelix as compared to GnRH agonists. The pharmacologic reasons for this difference are not completely understood but might reside in the suppression of FSH, with preservation of endothelial cell functions, and the inhibition of GnRH receptors on T-cells, which avoids an inflammatory process which finally disrupts atherosclerotic plaques.[8] In the present study we confirmed a difference in CV events between degarelix (4.1%) and GnRH agonists (9.6%), but the small sample size did not allow us to draw definitive conclusions.

As for bone complications, it has been demonstrated that bone health in PCa patients is already impaired before starting ADT: prevalence of osteoporosis/osteopenia in these patients goes from 35% to 58% and this condition is often underdiagnosed.[32] ADT, with testosterone suppression, leads to a quick increase of bone turnover with bone loss and qualitative/microstructural damage. As a consequence, pathologic fractures usually occur during first year of ADT.[32] As shown in Table 6, literature is unanimous in reporting an augmented risk of bone loss, osteoporosis and fractures with ADT. In our series, the rate of bone events was 7.3%; however, the real osteoporosis rate might be sensibly higher given that very few patients had undergone bone densitometry at baseline and during follow-up. Particular care should be given by urologist to the need of monitoring the levels of calcium and vitamin D and their supplementation, if needed.[32] The same goes for bone antiresorptive therapies,[8] that were given to only one-third of our patients with bone metastases. To overcome these issues, in our institution we have scheduled endocrinologic consultations for all patients under ADT, in order to monitor their bone health and metabolic status. A recent

Table 4. Main studies reporting CV risk in ADT patients.

Author	Type of study	Treatment	Patients	Outcomes
Bosco et al.[10]	Meta-analysis of eight studies	ADT (GnRHag, orchiectomy, antiandrogens)	Pts with PCa treated with ADT	The RR for any type of nonfatal CV events was 1.38 for GnRHag, 1.44 for orchiectomy, and 1.21 for antiandrogens. The association were stronger for myocardial infarction.
Gandaglia et al.[14]	Retrospective, from SEER database FU: 111 months	ADT (GnRHag, orchiectomy)	9.596pts with metastatic PCa treated with ADT within 6 months of diagnosis (3.049 with pre-existing CV disease)	5-year CV mortality rates 9.8% in general population and 14.8% in patients with pre-existing CV disease. 5-year CV mortality rates increase with age and comorbidities.
Gandaglia et al.[21]	Retrospective, from SEER database FU: 75 months	ADT (GnRHag, orchiectomy)	140.474 pts with non-metastatic PCa (59.995 with ADT and 80.479 with no ADT)	GnRHag but not orchiectomy was associated with higher risk of coronary artery disease (HR 1.11), acute myocardial infarction (HR 1.09) and sudden cardiac death (HR 1.18) in competing-risk multivariable analysis.
Haque et al.[11]	Prospective, from Kaiser Permanente Southern California FU: 3.4 years	ADT (GnRHag, antiandrogens, CAB)	7.637 pts with newly diagnosed PCa initially undergoing active surveillance (2.170 with ADT)	ADT was associated with increased risk of heart failure (aHR 1.81) in men without pre-existing CV disease; elevated risk of arrhythmia (aHR 1.44) and conduction disorder (aHR 3.11) were only observed in men with pre-existing CV disease.
Hui-Han et al.[22]	Retrospective, single-center FU: 1 year	ADT (GnRHag, antiandrogens, estrogens, ketoconazole) vs RP, RT, surveillance	3.050 pts with de novo PCa (1.244 with ADT, 1.806 with no ADT)	Heart failure rates per 100 person-years 4.00 for ADT users (aHR 1.92 in propensity score) and 1.89 for nonusers.
Keating et al.[23]	Retrospective, from Veterans Healthcare Administration FU: 1 year	ADT (GnRHag, antiandrogens, CAB, orchiectomy)	37.443 pts with local or regional PCa (14.597 with ADT)	GnRHag were associated with significantly increased risk of diabetes (aHR 1.28), coronary artery disease (aHR 1.19), myocardial infarction (aHR 1.28), sudden cardiac death (aHR 1.22). Antiandrogens were not associated with any of these outcomes.
Kohutek et al.[24]	Retrospective, single-center FU: 9.3 years	RT with and without ADT	2.211 pts with localized PCa treated with RT (991 with ADT, 1.220 without ADT)	Both ADT at the time of RT and the time of salvage were associated with increased CV risk (19.6% vs 14.3% at 10 years), as were age, diabetes, smoking and previous CV event.
Nead et al.[25]	Meta-analysis of 10 studies	ADT with and without estrogen	>250.000 pts on ADT with and without estrogen	Significant increase in risk of thromboembolic events in men with PCa on ADT without estrogens (HR 1.43) and with estrogens (HR 3.72)
Nguyen et al.[16]	Meta-analysis of eight RCTs	ADT with GnRHag	4.141 pts with non-metastatic PCa (2.200 on ADT vs 1.941 with no immediate ADT)	CV mortality in patients on ADT vs control was not significantly different. ADT was not associated with excess CV death in trials of ⩾3 years of ADT nor in trials of ⩽6 months of ADT
O'Farrell et al.[26]	Retrospective from PCBaSE Sweden FU: 4.4 years	ADT (GnRHag, antiandrogens, CAB, orchiectomy)	42.263 pts with PCa (all-stages) who received ADT as primary treatment or because of disease progression	GnRHag and orchiectomy have higher risk of thromboembolic disease than comparison cohort (HR 1.67). Antiandrogen monotherapy have lower risk of deep vein thrombosis (HR 0.49)
O'Farrell et al.[12]	Retrospective from PCBaSE Sweden FU: 4 years	ADT (antiandrogens, GnRHag, CAB, orchiectomy)	41.362 pts with PCa (all-stages) on ADT compared with 187.785 PCa-free comparison cohort	CV risk was increased in men on GnRHag (HR 1.21) and orchiectomy (HR 1.16) compared to the comparison cohort. Men on antiandrogens were at decreased risk. CV risk was highest during the first 6 months of ADT.
Smith et al.[27]	Pooled data from 17 trials	ADT (degarelix)	1.704 PCa pts on degarelix	Rates if CV events were similar before and after degarelix treatment; no association was found in multivariate model.
Voog et al.[28]	Retrospective, multicentric from RTOG 94 to 08 FU: 9.1 years	RT with our without short-course ADT (4-month GnRHag + flutamide)	1.979 pts with clinically localized PCa (987 ADT vs 992 no ADT)	ADT not associated with increased CV mortality (unadjusted HR 1.07 [CI 0.81–1.42]
Wallis et al.[29]	Retrospective, from SEER database FU: 6 years	Surgery with or without ADT vs RT with or without ADT	60.156 pts with clinically localized PCa (14.403 surgery, of whom 1.681 +ADT; 45.753 RT, of whom 23.882 +ADT)	ADT (aHR 1.18–1.32) and RT (aHR 1.16–1.28) associated with increased risk of coronary heart disease and sudden cardiac death
Ziehr et al.[13]	Retrospective, single-center FU: 4.8 years	Brachytherapy with or without neoadj ADT (GnRHag)	5.077 pts with clinically localized PCa (1.521 ADT vs 3.556 no ADT)	ADT associated with 5% absolute 5-year CV mortality excess risk only in men with prior CHF or MI (7.01% for ADT vs 2.01% vs no ADT)

Table 5. Main studies reporting CV risk in ADT patients, comparing GnRH agonists and GnRH antagonists.

Abufaraj et al.[30]	Meta-analysis of eight RCTs	ADT (GnRHag vs GnRHant)	2.632 pts with PCa (986 with GnRHag vs 1.646 with GnRHant)	GnRHant associated with fewer CV events (RR 0.52), higher injection site reaction rates
Albertsen et al.,[8]	Pooled analysis of six RCTs FU: 3/14 months	ADT (GnRHag vs GnRHant)	2.328 pts with PCa on ADT	GnRHant associated with lower CV risk (HR 0.44) than GnRHag
Hupe et al.[31]	Retrospective, from German database FU: ⩾1 year	ADT (GnRHag vs GnRHant)	2.382 pts with PCa on ADT	No significant differences in the incidence of diabetes, CV disease, nor mortality rates between GnRHag and GnRHant. Significant increase in hypertension for GnRHag.
Perrone et al.[18]	Retrospective, from regional Italian databases FU: 1 year	ADT (GnRHag vs GnRHant)	9.785 pts with PCa (9.158 with GnRHag vs 627 with GnRHant)	Incidence of CV events significantly higher in pts with GnRHag rather than GnRHant (8.8 vs 6.2, risk of CV events lower for GnRHant (HR 0.76), even in the subgroup without previous CV events.
Scailteux et al.[19]	Retrospective, from French Health Insurance data	ADT (GnRHag, antiandrogens, CAB, orchiectomy)	35.118 pts with PCa	CAB associated with increased risk (aHR 1.6) and AA with decreased risk (aHR 0.6) of ischemic events when compared to GnRHag. No significant association found with GnRHant. Probability of clinically meaningful difference when comparing GnRHag and GnRHant appears rather low.

Table 6. Main studies reporting bone health risk in ADT patients.

Author	Type of study	Treatment	Patients	Outcomes
Abufaraj et al.[30]	Meta-analysis of eight RCTs	ADT (GnRHag vs GnRHant)	2.632 pts with PCa (986 with GnRHag vs 1.646 with GnRHant)	GnRHant associated with fewer musculo-skeletal events including back pain, myalgia, arthralgia, spinal cord stenosis, fracture (RR 0.76)
Dalla Via et al.[34]	Cross-sectional	ADT	70 ADT-treated, 52 PCa controls, 70 healthy controls	ADT associated with lower BMD and estimated compressive bone strength, particularly at trabecular skeletal sites. No consistent differences in cortical bone structure, distribution, or bending strength
Kawahara et al.[35]	Retrospective, single-center	Brachitherapy, RP, RT, ADT	1.220 PCa patients (187 ADT vs 399 no ADT)	ADT duration correlated with major osteoporotic risk and hip fracture risk; major fracture risk was 20% higher for ADT and hip fracture risk 3% higher
Sharma et al.[36]	Systematic review of nine studies	ADT	3.704 patients of localized, metastatic, castration resistant PCa with or without ADT	ADT and advanced age were the most robust risk factors to influence FRAX score
Wallis et al.[29]	Retrospective, using SEER database FU: 6 years	Surgery with or without ADT vs RT with or without ADT	60.156 pts with clinically localized PCa (14.403 surgery, of whom 1.681 +ADT; 45.753 RT, of whom 23.882 +ADT)	ADT and RT associated with increased risk of fracture and fracture requiring re-hospitalization

ADT: androgen deprivation therapy; ag: agonist; ant: antagonist; BMD: bone mineral density; CAB: combined androgen blockade; CV: cardiovascular; FU: follow-up; GnRH: Gonadotropin Releasing Hormone; PCa: prostate cancer; RCT: randomized clinical trial; RP: radical prostatectomy; RT: radiotherapy.

American economic analysis has shown that emergency department visits were twice as frequent and hospitalization four times as frequent in patients with bone metastases who had experienced at least one bone event, with an attributable cost of one skeletal event of €21,191.[33]

Finally, all other complications including metabolic ones were reported in around 20% of our patients. While is well-known the association between ADT and diabetes, dyslipidemia, metabolic syndrome, and weight gain,[37] it is difficult to retrospectively evaluate the worsening of glycemic or lipid profile. Depression has also been linked to ADT,[38] but this side effect was clearly reported by only one of our patients. On the other hand, fatigue, muscular weakness, hot flushes, and sweating were frequently reported. We must not forget hyporegenerative anemia, which sometimes requires blood transfusion or erythropoietin, and gynecomastia. Only one patient treated with degarelix suffered of injection site reaction.

As previously highlighted, this study is affected by several limitations inherent to its retrospective nature, mainly due to the lack of precious data such as causes of death, minor CV events, bone densitometries results, or precise

metabolic evaluations. The lack of assessment of functional status, frailty, and comorbidity index at initial assessment is another major limitation, together with the relatively small sample size. On the other hand, though, this study provides a clear snapshot of the management of PCa patients on ADT in a uro-oncological referral center, and its pitfalls. Several suggestions arise from the analysis of our findings: first, the adoption of a standardized report of ADT-related complications is recommended for all patients undergoing ADT, to guarantee an adequate medical monitoring; second, a cardiologic and endocrinologic consultation should be advised at ADT onset. Third, an adequate evaluation of the frailty status of the patient should be done in all elderly, reserving radical approaches for those who are fit in spite of their age.

Conclusions

In an Italian referral center, most ADT prescriptions followed EAU guidelines, but a non-negligible proportion still did not fall within these indications, exposing patients to unnecessary side effects. Compliance to ADT was generally good with a predominant use of GnRH agonists. Tolerance to ADT was fair, even if standardized reports were lacking.

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References

1. EAU Guidelines. Edn. Presented at the EAU Annual Congress Milan 2021. ISBN 978-94-92671-13-4.
2. Morgia G, Russo GI, Tubaro A, et al. Prevalence of cardiovascular disease and osteoporosis during androgen deprivation therapy prescription discordant to EAU guidelines: results from a multicenter, cross-sectional analysis from the CHOsIng treatment for prostate canCEr (CHOICE) study. *Urology* 2016; 96: 165–170.
3. Miller KD, Nogueira L, Mariotto AB, et al. Cancer treatment and survivorship statistics, 2019. *CA Cancer J Clin* 2019; 69: 363–385.
4. Nguyen PL, Alibhai SM, Basaria S, et al. Adverse effects of androgen deprivation therapy and strategies to mitigate them. *Eur Urol* 2015; 67: 825–836.
5. Zareba P, Duivenvoorden W, Leong DP, et al. Androgen deprivation therapy and cardiovascular disease: what is the linking mechanism? *Ther Adv Urol* 2016; 8: 118–129.
6. Tivesten Å, Pinthus JH, Clarke N, et al. Cardiovascular risk with androgen deprivation therapy for prostate cancer: potential mechanisms. *Urol Oncol* 2015; 33: 464–475.
7. Lomax AJ, Parente P, Gilfillan C, et al. "First, do no harm": managing the metabolic impacts of androgen deprivation in men with advanced prostate cancer. *Intern Med J* 2016; 46: 141–148.
8. Albertsen PC, Klotz L, Tombal B, et al. Cardiovascular morbidity associated with gonadotropin releasing hormone agonists and an antagonist. *Eur Urol* 2014; 65: 565–573.
9. Walz S, Maas M, Stenzl A, et al. Bone health issues in patients with prostate cancer: an evidence-based review. *World J Mens Health* 2020; 38: 151–163.
10. Bosco C, Bosnyak Z, Malmberg A, et al. Quantifying observational evidence for risk of fatal and nonfatal cardiovascular disease following androgen deprivation therapy for prostate cancer: a meta-analysis. *Eur Urol* 2015; 68: 386–396.
11. Haque R, UlcickasYood M, Xu X, et al. Cardiovascular disease risk and androgen deprivation therapy in patients with localised prostate cancer: a prospective cohort study. *Br J Cancer* 2017; 117: 1233–1240.
12. O'Farrell S, Garmo H, Holmberg L, et al. Risk and timing of cardiovascular disease after androgen-deprivation therapy in men with prostate cancer. *J Clin Oncol* 2015; 33: 1243–1251.
13. Ziehr DR, Chen MH, Zhang D, et al. Association of androgen-deprivation therapy with excess cardiac-specific mortality in men with prostate cancer. *BJU Int* 2015; 116: 358–365.
14. Gandaglia G, Sun M, Popa I, et al. Cardiovascular mortality in patients with metastatic prostate cancer exposed to androgen deprivation therapy: a population-based study. *Clin Genitourin Cancer* 2015; 13: e123–e130.
15. Gupta D, Salmane C, Slovin S, et al. Cardiovascular complications of androgen deprivation therapy for prostate cancer. *Curr Treat Options Cardiovasc Med* 2017; 19: 61.
16. Nguyen PL, Je Y, Schutz FA, et al. Association of androgen deprivation therapy with cardiovascular death in patients with prostate cancer: a meta-analysis of randomized trials. *JAMA* 2011; 306: 2359–2366.
17. Eurostat Statistics Explained. Archive: people in the EU-population projections. Revision as of 31 October 2017. Accessed August 11, 2021. https://ec.europa.eu/eurostat/statistics-explained/index.php?oldid=358171&title=People_in_the_EU_%E2%80%93_population_projections
18. Perrone V, Degli Esposti L, Giacomini E, et al. *Ther Clin Risk Manag* 2020; 16(16): 393–401.
19. Scailteux LM, Vincendeau S, Balusson F, et al. Androgen deprivation therapy and cardiovascular risk: no meaningful difference between gnrh antagonist and agonists-a nationwide population-based cohort study based on 2010-2013 French health insurance data. *Eur J Cancer* 2017; 77: 99–108.
20. Crawford ED, Heidenreich A, Lawrentschuk N, et al. Androgen-targeted therapy in men with prostate cancer:

evolving practice and future considerations. *Prostate Cancer Prostatic Dis* 2019; 22: 24–38.
21. Gandaglia G, Sun M, Popa I, et al. The impact of androgen-deprivation therapy (ADT) on the risk of cardiovascular (CV) events in patients with non-metastatic prostate cancer: a population-based study. *BJU Int* 2014; 114: E82–E89.
22. Hui-Han K, Li-Ting K, I-Hsun L, et al. Androgen deprivation therapy use increases the risk of heart failure in patients with prostate cancer: a population-based cohort study. *J Clin Pharmacol* 2019; 59: 335–343.
23. Keating NL, O'Malley AJ, Freedland SJ, et al. Diabetes and cardiovascular disease during androgen deprivation therapy: observational study of veterans with prostate cancer. *J Natl Cancer Inst* 2010; 102: 39–46.
24. Kohutek ZA, Weg ES, Pei X, et al. Long-term impact of androgen-deprivation therapy on cardiovascular morbidity after radiotherapy for clinically localized prostate cancer. *Urology* 2016; 87: 146–152.
25. Nead KT, Boldbaatar N, Yang DD, et al. Association of androgen deprivation therapy and thromboembolic events: a systematic review and meta-analysis. *Urology* 2018; 114: 155–162.
26. O'Farrell S, Sandström K, Garmo H, et al. Risk of thromboembolic disease in men with prostate cancer undergoing androgen deprivation therapy. *BJU Int* 2016; 118: 391–398.
27. Smith MR, Klotz L, van der Meulen E, et al. Gonadotropin-releasing hormone blockers and cardiovascular disease risk: analysis of prospective clinical trials of degarelix. *J Urol* 2011; 186: 1835–1842.
28. Voog JC, Paulus R, Shipley WU, et al. Cardiovascular mortality following short-term androgen deprivation in clinically localized prostate cancer: an analysis of RTOG 94-08. *Eur Urol* 2016; 69: 204–210.
29. Wallis CJ, Mahar AL, Satkunasivam R, et al. Cardiovascular and skeletal-related events following localized prostate cancer treatment: role of surgery, radiotherapy, and androgen deprivation. *Urology* 2016; 97: 145–152.
30. Abufaraj M, Iwata T, Kimura S, et al. Differential impact of gonadotropin-releasing hormone antagonist versus agonist on clinical safety and oncologic outcomes on patients with metastatic prostate cancer: a meta-analysis of randomized controlled trials. *Eur Urol* 2021; 79: 44–53.
31. Hupe MC, Hammerer P, Ketz M, et al. Retrospective analysis of patients with prostate cancer initiating GNRH agonists/antagonists therapy using a German claims database: epidemiological and patient outcomes. *Front Oncol* 2018; 8: 543.
32. Santini D, Berruti A, Di Maio M, et al. Bone health management in the continuum of prostate cancer disease: a review of the evidence with an expert panel opinion. *ESMO Open* 2020; 5: e000652.
33. McDougall JA, Bansal A, Goulart BH, et al. The clinical and economic impacts of skeletal-related events among medicare enrollees with prostate cancer metastatic to bone. *Oncologist* 2016; 21: 320–326.
34. Dalla Via J, Daly RM, Owen PJ, et al. Bone mineral density, structure, distribution and strength in men with prostate cancer treated with androgen deprivation therapy. *Bone* 2019; 127: 367–375.
35. Kawahara T, Fusayasu S, Izumi K, et al. Bone management in Japanese patients with prostate cancer: hormonal therapy leads to an increase in the FRAX score. *BMC Urol* 2016; 16: 32.
36. Sharma A, Sinha RJ, Singh V, et al. Implications of the Fracture Risk Assessment Algorithm for the assessment and improvement of bone health in patients with prostate cancer: a comprehensive review. *Turk J Urol* 2019; 45: 245–253.
37. Patil T and Bernard B. Complications of androgen deprivation therapy in men with prostate cancer. *Oncology* 2018; 32: 470–474.
38. Nead KT, Sinha S, Yang DD, et al. Association of androgen deprivation therapy and depression in the treatment of prostate cancer: a systematic review and meta-analysis. *Urol Oncol* 2017; 35: 664.e1–664.e9.